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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/510,249

04/11/2005

Karin A Connors

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EXAMINER

BAGGOT, BRENDAN O

ART UNIT

PAPER NUMBER

1638

MAIL DATE

DELIVERY MODE

06/12/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/510,249	Applicant(s) CONNORS ET AL.	
	Examiner BRENDAN O. BAGGOT	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 December 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9 is/are pending in the application.
- 4a) Of the above claim(s) 9 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on 01 October 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/16/05 8/10/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Restriction / Election

1. The Office acknowledges the receipt of Applicant's election restriction filed 20 December 2007. Applicant elects Group I, claims 1-8 drawn to a method of obtaining flavonoids, with traverse. In the interest of economy of prosecution, Groups I and II are rejoined. Applicant's traversals are therefore moot for the following reasons: mutant will be examined. Group III is withdrawn from further consideration.

2. Claims 1-8 are examined in the instant action.

Claim Objections

3. Claim 1 and its dependents 2-8 are objected to because of the following informalities: "ANT1" is an abbreviation or acronym. It is suggested that the full name should be spelled out once upon first appearance in the claims i.e. Anthocyanin 1 (ANT1), after that it would be appropriate to use the acronym. Appropriate correction is required. See definition from specification provided below. (See paragraph 35).

[0035] The terms "Anthocyanin 1" and "ANT1", as used herein encompass native Anthocyanin 1 (ANT1) nucleic acid and amino acid sequences, homologues, variants and fragments thereof.

4. Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the

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claim(s) in independent form. Applicant defines ANT1 as set forth above. Said definition does not encompass “mutant.” Thus, claim 3 is broader than claim 1 because it encompasses mutants not encompassed by claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of obtaining or isolating the anthocyanins listed in Table 2 from tomato, the anthocyanins cyanidine-3-glucoside and cyanidine-3-rutinoside from tobacco, and glycitein (an isoflavone) from tomato (Specification pages 33-34 and 36-37; specification pages 20, 31-32, 36-37 and 38), does not reasonably provide enablement for a method of obtaining *any flavonoid* or *any isoflavone in any plant*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Claim 1 is broadly drawn to a method of obtaining *any flavonoid* of any structure made in *any plant* overexpressing ANT1. The claims breadth includes a method of obtaining any *flavanones*, *aurones* or *isoflavones*.

In contrast, the specification only provides guidance for: a method of obtaining anthocyanins wherein the plant is tomato, and wherein the tomato produces an anthocyanin selected from the group consisting of delphinidin 3-rutinoside-5-glucoside, delphinidin 3-

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(coumaroyl) rutinose-5-glucoside, delphinidin 3-(caffeoyl) rutinose-5-glucoside, petunidin 3-rutinose-5-glucoside, petunidin 3-(coumaroyl) rutinose-5-glucoside, petunidin 3-(caffeoyl) rutinose-5-glucoside, malvidin 3-rutinose-5-glucoside, malvidin 3-(coumaroyl) rutinose-5-glucoside, and malvidin 3-(caffeoyl) rutinose-5-glucoside; a method of isolating glycitein (an isoflavone) from ANT1 overexpressing tomato plants. Applicant also teaches a method of obtaining cyanidine-3-glucoside and cyanidine-3-rutinose anthocyanins from ANT1 overexpressing tobacco plants. (Specification pages 33-34 and 36-37; 20, 31-32, 36-37 and 38).

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B.S.J. WINKEL

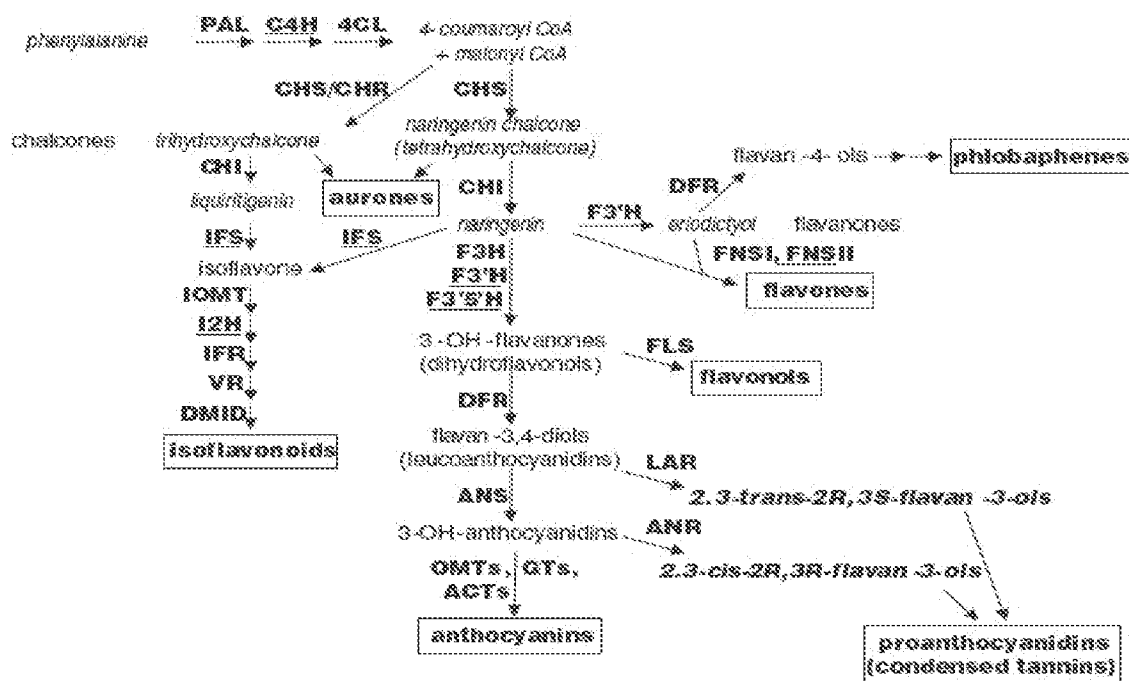


Figure 3.1 Schematic of the flavonoid pathway showing the enzymatic steps leading to the major classes of end products, flavonols, anthocyanins, proanthocyanidins, phlobaphenes, aurones, flavones, and isoflavonoids, which are identified with boxes. Names of the major classes of intermediates are given, with names of specific compounds in *italics*. Enzymes are indicated with standard abbreviations in **bold**; names of cytochrome P450 monooxygenases that may function as membrane anchors for other flavonoid enzymes are underlined. Abbreviations: ACTs, acetyl transferases; ANR, anthocyanidin reductase; ANS, anthocyanidin synthase (also known as leucoanthocyanidin dioxygenase); C4H, cinnamate 4-hydroxylase; CHI, chalcone isomerase; CHR, chalcone reductase; CHS, chalcone synthase; 4CL, 4-coumaroyl-CoA-ligase; DFR, dihydroflavonol 4-reductase; DMID, 7,2'-dihydroxy, 4'-methoxyisoflavanol dehydratase; F3H, flavanone 3-hydroxylase; FNSI and FNSII, flavone synthase I and II; F3'H and F3'5'H, flavanoid 3' and 3'5' hydroxylase; IOMT, isoflavone O-methyltransferase; IFR, isoflavone reductase; I2'H, isoflavone 2'-hydroxylase; IFS, isoflavone synthase; LAR, leucoanthocyanidin reductase; OMTs, O-methyltransferase; PAL, phenylalanine ammonia-lyase; GTs, glucosyl transferases; VR, vestitone reductase.

Figure 1, taken from *The Science of Flavonoids*, 2006, page 72.

Applicant does not teach a method of obtaining *any flavonoid* or any *isoflavone* (other than glycitein) from any plant. Applicant does not teach a method of obtaining any *flavanones*, any *aurones*, or any *anthocyanins*. Applicant does not teach any working examples of obtention of any *flavanones*, *aurones* or *anthocyanins*.

Applicant does not teach a method of obtaining any flavanone-type flavonoid in any plant species that do not produce flavanones because they do not possess a flavonoid 3'-hydroxylase (F3'H) and/or a flavonoid 3',5'-hydroxylase (F3'5'H) (e.g., horsetails, flowering plant angiosperms, gnetophyta, conifers, cycads, or club mosses); or for a method of producing any aurone-type flavonoid in any plant species that do not produce aurones because they do not possess an aureusidin synthase (AUS) (e.g., all plants except for flowering plant-angiosperms); or for a method of producing any anthocyanin-type flavonoid in any plant species that do not produce anthocyanin because they do not possess an anthocyanidin synthase (ANS) (e.g., ferns). (See *The Science of Flavonoids*, Erich Grotewold, (2006), Springer Science + Business Media, Inc., New York, New York; Figures 7.2, 3.1, 5.1, 6.1, and 8.1).

The term flavonoid is an extremely broad term covering at least 7 different chemical classes: flavone, flavonol, flavonone, isoflavone, anthocyanin, aurones, phlobaphene, flavone, proanthocyanidins and possibly other yet undiscovered chemical classes.

The state-of-the-art for anthocyanin phenotype producing proteins having consistent behavior across different species is unpredictable. A myc-type R protein from *Arabidopsis*, that showed significant homology to the Lc maize R-type myc transcription factor, did not induce anthocyanin biosynthesis when transformed into pea (an isoflavonoid producing plant)

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demonstrating that anthocyanin phenotype producing transcription factors have unknown and divergent roles in regulating anthocyanin or isoflavonoid biosynthetic metabolism in plants and thus may not regulate anthocyanin or isoflavonoid biosynthetic pathways because of evolutionary divergence in the manner in which those pathways are regulated (de Pater S. *et al.* Plant Molecular Biology, 1997; Vol. 34, 169-174; See Abstract and page 173 column 1 line 12 to column 2 line 3).

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M.D. KAUSER

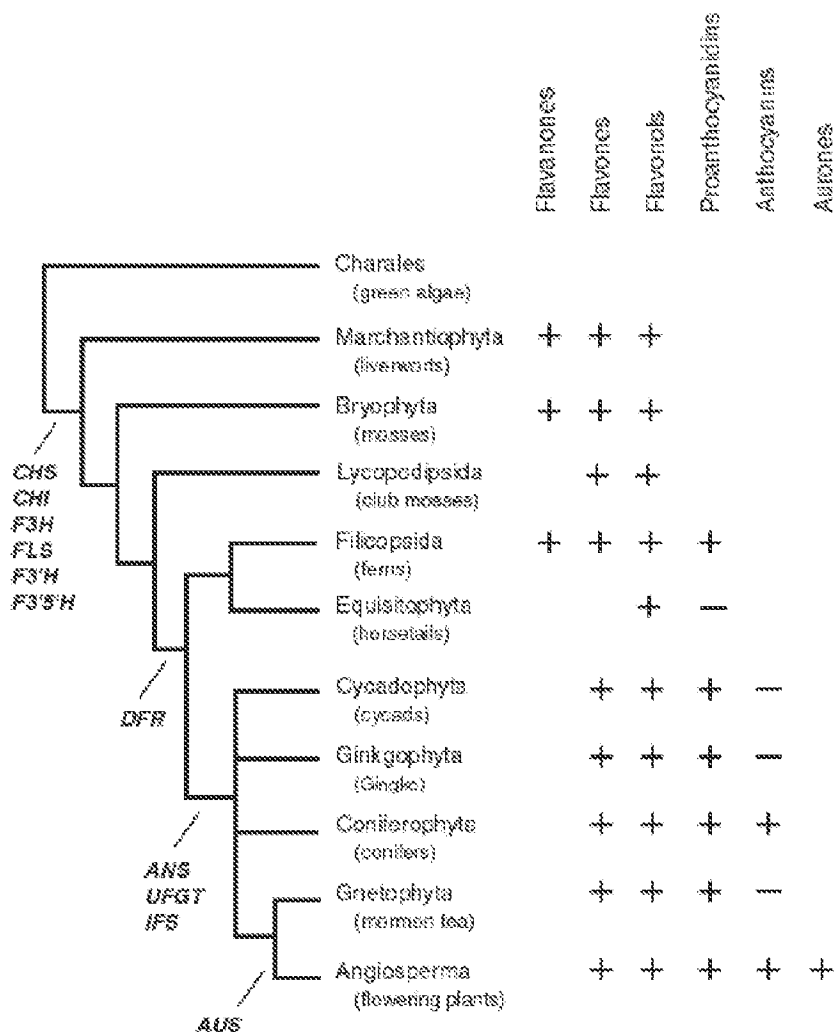


Figure 7.2 Land plant phylogeny showing the time of origin of flavonoid enzymes. +, Documented presence of flavonoid; —, possible evolutionary loss of flavonoid. Phylogeny from Savolainen and Chase (2003).

In contrast to flavonols, isoflavonoids occur only sporadically throughout the land plants (Dewick, 1988). Isoflavonoids have been reported in the moss *Bryum*

Figure 2: taken from *The Science of Flavonoids*, 2006, page 180.

Further, the state of the art for producing any number of isoflavonoids in non-isoflavonoid producing plants is unpredictable because enzymes such as chalcone isomerase in non-leguminous plants do not use isoliquiritigenin and therefore expressing an ANT1 enzyme to

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form an isoflavone in a non-leguminous plant would not result in the production of genistein or daidzein. Thus, the type of isoflavone produced via transgenic expression of ANT1 is plant specific. Furthermore, the researchers did not report the production of daidzein in the non-leguminous *Arabidopsis* species when transformed with the leguminous sequence encoding isoflavone synthase from soybean and chalcone isomerase from alfalfa suggesting that there are unforeseen mechanisms regulating flux through the flavonoid pathways in non-leguminous plants that would prevent engineering isoflavone production (Liu C. *et al.* PNAS, 2002, Vol. 99, No. 22; pp. 14578-14583; see page 14850, column 2 lines 26-37; and page 14581 Table 1). Grotewald, as shown in Figure 2 above, teaches that “isoflavonoids occur only sporadically throughout the land plants.” Thus, expression of ANT1 – a transcription factor which turns on certain anthocyanin genes – in isoflavoneless land plants could not possibly cause the production of isoflavones because the isoflavone biosynthetic enzymes DO NOT exist in said land plant and ANT1 expression does not provide for said expression. (*See The Science of Flavonoids*, Erich Grotewald, (2006), Springer Science + Business Media, Inc., New York, New York; Figure 7.2, page 180).

Finally, the state of the art for producing any flavonoid via ANT1 overexpression is unpredictable. According to *some of the inventors*, overexpression of ANT1 *failed to produce ANY flavonoid*. Mathews *et al.* teach that *ant1* lines showed intense purple pigmentation reflecting activation of the anthocyanin pathway via the overexpression of ANT1, a MYB transcription factor. Mathews also reports the detection of 9 different anthocyanins in *ant1* transformed tomato but no flavonoids other than those in Table 2. For example, Mathews DOES NOT TEACH a method of obtaining any *flavanones*, *aurones* or *isoflavones* via overexpression

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of ANT1. In addition, Mathews teaches that [only] “. . . early and late . . . anthocyanin synthesis [genes] CHS and DFR were upregulated in ANT1-overexpressing plants.” (Mathews *et al.*

Activation Tagging in Tomato Identifies a Transcriptional Regulator of Anthocyanin

Biosynthesis, Modification and Transport the Plant Cell, Vol. 15, 1689–1703, August 2003; see abstract, p. 1695, right col., first paragraph).

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue trial and error experimentation would be required to practice the claimed invention, and therefore the invention is not enabled throughout the broad scope of the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed.Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed.Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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6. Claims 1-8 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-11 of U.S. Patent No. 7,304,207. Although the conflicting claims are not identical, they are not patentably distinct from each other because the first two steps recited in claim 5 before the “, and extracting anthocyanin from the plant” are obvious over the limitation of instant claim one: “obtaining flavonoids . . . [by] obtaining a plant that overexpresses ANT1 Compared to wild type plants . . .” and vice versa. One of skill in the art would have immediately recognized the interchangeability of the terms “isolating” and “obtaining”. Applicant has collapsed all the first two steps recited in claim 5 into the first step of instant claim 1. The method step of isolating flavonoids by size is not patentably distinct from the method step of isolating anthocyanins by size.

US Patent No. 7,304,207	Instant Claim 1
<p>5. A method of isolating an <i>anthocyanin</i> from a plant, said method comprising introducing into progenitor cells of the plant a plant transformation vector comprising a nucleic acid sequence which encodes an ANT1 polypeptide having at least 95% sequence identity to the amino acid sequence SEQ ID NO: 2, growing the transformed progenitor cells to produce a transgenic plant having an ANT1 phenotype that expresses the polynucleotide sequence comprised by the vector, and extracting the anthocyanin from the plant. (Emphasis added).</p>	<p>1. (Currently amended) A method of obtaining <i>flavonoids</i> comprising- obtaining a plant that overexpresses ANT 1 compared to wild-type plants[.]; and extracting a flavonoid from the plant. (Emphasis added).</p>

Remarks

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7. Claims 1-8 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brendan O. Baggot whose telephone number is 571/272-5265. The examiner can normally be reached on Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571/272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Anne Marie Grunberg/

Supervisory Patent Examiner, Art Unit 1638